Matching the Market for Heart Transplantation

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Abstract—Heart transplantation is the most effective therapy for patients with Stage D heart failure with a median life expectancy of ≈10 to 15 years.1 Unfortunately, many patients die on the waiting list hoping for a chance of survival. The life boat cannot rescue everyone. Over a decade, the donor pool has remained relatively stable, whereas the number of heart transplant candidates has risen. Potential recipients often have many comorbidities and are older because the criteria for heart transplantation has few absolute contraindications. Women, Hispanics, and patients with restrictive heart disease and congenital heart disease are more likely to die while awaiting heart transplantation than men, white patients, and those with either ischemic or dilated cardiomyopathy. To better match the market, we need to (1) increase the donor pool, (2) reduce the waitlist, and (3) improve the allocation system. This review article addresses all 3 options and compares strategies in the United States to those in other countries. (Circ Heart Fail. 2016;9:e002679. DOI: 10.1161/CIRCHEARTFAILURE.115.002679.)

Key Words: health care ■ heart disease ■ heart failure ■ transplantation ■ ventricular assist device

Heart transplantation is the most effective therapeutic treatment for end-stage heart failure with a median survival of 10 to 15 years.1 Unfortunately, the number of donors does not match the number of people with Stage D heart failure who could benefit. With advances in technology, mechanical circulatory support has successfully bridged numerous patients to heart transplantation. However, many advanced heart failure patients still die on the waitlist. This article will review 3 options that should be pursued simultaneously to better match the market: (1) increase the donor pool, (2) reduce the waitlist, and (3) improve the allocation system.

History of Transplantation

The first successful heart transplantation in the United States (US) was performed in 1968, which was more than a decade after the first successful cadaveric kidney transplantation.2 During this time, developments included the utilization of tissue typing for matching and advancements in immunotherapy. That same year, the first organ procurement organization was established in Boston, and the Uniform Anatomic Gift Act enabled adults to register as organ donors with a Uniform Donor Card. In 1984, Congress passed the National Organ Transplant Act enabling the establishment of the Organ Procurement and Transplantation Network to ensure fair and equitable allocation of organs and the Scientific Registry of Transplant Recipients to evaluate transplant data. The United Network for Organ Sharing (UNOS) was awarded the Organ Procurement and Transplantation Network contract in 1986 and formalized the heart transplant allocation system. Allocation was to be based on severity of illness and time on a national waitlist.3 National guidelines for selection and treatment of heart transplant candidates were created in the early 1990s4,5 and remain similar to the most current guidelines updated in 2016.6 Median survival post heart transplantation has advanced from 15 to 18 days to 11 years because of improvements in immunotherapy and antibiotics.1,7 However, this life-saving option continues to be limited by the number of donor hearts available, which has remained in the range of 2000 to 2700 in the United States for the past 15 years.8 The number of patients on the waiting list as of January 29, 2016, is over 4000, almost 2-fold higher than the number of patients who will actually undergo heart transplantation.8 Consequently, waiting times continue to increase and can be beyond a year even for patients considered to have the most urgent illness. Therefore, the time has come to better match the market of supply and demand for heart transplantation.

Matching the Market

Donor Pool

There are 2 ways to increase the donor pool: (1) increase rate of organ donation and (2) increase organ donor utilization. Increasing organ donation requires registering more healthy people in the donor organ program via presumed consent (opt-out system), incentives, or awareness campaigns. Increasing donor utilization, on the contrary, requires accepting marginal donors that seem high risk and accepting donors that are high risk but may be suitable under special circumstances.

Increasing Rate of Suitable Donors

Opt-Out System

The US currently works on an opt-in system where people at time of obtaining a driver’s license can decide to opt-in to register as an organ donor. The alternative is an opt-out system.
where people are assumed organ donors unless they opt-out. In some countries (ie, Austria), opt-out is a hard stop rule that on death no member of the family can change, and in other countries (ie, France, Belgium), opt-out is a soft stop rule that can be changed if family members oppose at time of death.

The opt-out system quickly increases the list of potential organ donors but has had varied success in actually increasing the number of patients transplanted in a given country. For instance, Spain has an opt-out system and has one of the highest rates of organ donations in Europe. Singapore, on the other hand, has an opt-out system since 1987, yet performed only 4 heart transplantations in 2007 with a total of 26 organ donations that year. So why does one country succeed and another fail?

Spain adopted an opt-out policy in 1979 but did not experience clinically significant increases in donation rates for 10 years after implementation. By the early 1990s, heart transplantations rose from 10 performed in 1984 to >230 performed per year since 1992. Spain’s current success is because of developing processes for early identification of brain death, referral of potential donors with an expanded donor pool, usage of hospital-based transplant coordinators to discuss the importance of donation with family members, quality assurance programs (internal and external) to monitor the process, and a centralized single transplant waiting list. Although all these factors contributed to Spain’s success, the greatest impact was achieved after the government in 1989 supported a transplant coordinator in every hospital to facilitate the process, and a centralized single transplant waiting list. In other countries like Spain, the third party is transplant coordinators. In the United States, the third party is an organ procurement organization, and in other countries like Spain, the third party is transplant coordinators. The third party often is necessary to improve the rate of consent from families for donation from the deceased. A medical care provider must quickly stabilize a potential donor and establish a relationship with the family to gain trust. It is hard for the provider at a time of emotional distress for the family to convey medical futility and request for organ donation. Therefore, a third party is helpful to prevent conflicts of interest and provide a lower priority to first-degree relatives of registered organ donors because research suggested that registered donors were more likely to consent to organ donation of a deceased relative when wishes were not specified. Although it remains too soon to know the full potential of Israel’s positive incentive program, there has been an increase in organ donation rate from 7.8 donors per million populations in 2010 to 11.4 donors per million populations in 2011.

Financial or healthcare incentives have been provided to promote organ donation in a few countries, although almost all efforts have been dedicated toward living donors. In the United States, some states have arranged paid leave of absence for living donor-related activities and tax benefits. In other countries, Iran, for example, living donor support includes $4000 US (paid mostly by recipient) and 1-year coverage of medical insurance and hospital bills. Cadaveric organ donation is usually deemed altruistic and without incentives, although occasionally in Iran, money has been given to cover funeral expenses. Other countries such as Singapore and Chile have applied negative incentives to improve organ donation. For instance, people not willing to donate organs are assigned a lower priority to receive organs if/when needed. Although this negative transplant/donor contingency may provide similar result as a positive incentive program, they are different. The goal of the positive incentive program is to increase the number of registered organ donors with willing participants before their death, while the negative incentive program does not increase voluntary participants but does punish those not willing to donate organs. Which system is better may depend on the cultural composition within a given country and whether religious beliefs prevent organ donation, regardless of any incentive program.

### Third Party Advocates

A third party is often necessary to improve the rate of consent from families for donation from the deceased. A medical care provider must quickly stabilize a potential donor and establish a relationship with the family to gain trust. It is hard for the provider at a time of emotional distress for the family to convey medical futility and request for organ donation. Therefore, a third party is helpful to prevent concerns regarding potential conflict of interest. In the United States, the third party is an organ procurement organization, and in other countries like Spain, the third party is transplant coordinators. The specialized training of this third party to approach next-of-kin and the usage of quality assurance programs to monitor the process often determine the success rate of organ donation.
Awareness Campaigns

There have been several initiatives in the United States to increase donations and organ utilization rates by educating healthcare professionals and the public. Because of regional/hospital variations in performance, there have been publications on best practice (The Organ Donation Breakthrough Collaborative initiated by US Secretary of Health and Human Services, Tommy G Thompson).23 campaigns to increase public awareness through donor education outreach programs, including the Dow Take Initiative Program, brochures, donor education videos, and college donor awareness programs.25 State policies have also been created to educate the public, create donor recruitment activities, provide tax incentives, and provide paid leave of absence for living donors. Nearly all of these have had little impact.18 At a federal level, the Health Resources and Services Administration has supported organ donations through the National Organ Transplant Act, grant funding to support education for improvement in organ donations, and Surgeon General Antonia Novella’s Workshop on Increasing Organ Donation.26,27 Although some of the efforts above have improved donation rates locally,25 the number of heart transplants used nationally remained similar for almost 2 decades.8

Recently, popular media like Facebook have made a significant contribution to donor registration (see Figure 1).28 The launching of the Facebook organ donor initiative in 2012 correlated in time with an increase in heart transplantation. (From 1990 to 2011, there was a 9% increase in heart transplantation. Between 2011 and 2014, the number of heart transplants increased by 14%.)9 Facebook’s success was likely based on its wide usage and positive peer pressure when friends in a network were made aware of a new donor status.

Increasing Donor Utilization

Increasing the market via accepting marginal donors assumes there is an ideal donor and characteristics that identify high-risk donors. Furthermore, it implies that transplanting a marginal donor organ would result in poor outcome. How much do we really know?

Most centers consider an ideal donor as <40 years of age with no coronary artery disease, no structural heart disease, including left ventricular hypertrophy, nondiabetic, and with no cancer. The donor also should not have human immunodeficiency virus, hepatitis B or C, or any high-risk behavior, such as history of drug abuse or recent incarceration. Ischemic time should be <4 hours.

Undesirable donors should be separated into 2 categories: (1) adequate donors with some features suggestive of high risk and (2) true marginal donors. There are several donor characteristics that appear risky that are likely adequate and other risk factors that are a concern only when combined with other characteristics. For instance, high-risk donor characteristics requiring informed consent from the recipient because of concern of transmitting an infection include history of illicit intravenous drug usage, incarceration, hemophilia, exposure to human immunodeficiency virus, prostitution, and other high-risk sexual activity. However, the risk of transmission of an infection for all organ transplantations is only estimated to be <1%.29 Prior usage of cocaine30,31 by donors was once deemed undesirable, yet the data supporting this is now controversial.30,31 Left ventricular hypertrophy >1.3 cm and allograft ischemic times ≥4 hours is associated with high mortality, whereas mild left ventricular hypertrophy ≤1.3 cm and long ischemic times are not (see Figure 2).32 Diabetes mellitus or hypertension in male donors has a higher risk than when present in female donors (see Figure 3). Finally, undersizing the donor heart is most concerning when donor age >30 years in male donors/recipients and donor age >40 years in female donors/recipients.33 All these examples are deemed high risk, yet provide potentially usable organs.

What are true marginal donors? The characteristics of marginal donors were recently evaluated using Organ Procurement and Transplantation Network data between 1995 and 2010. Of the 82053 potential donors, only 36% were transplanted. The characteristics of rejected donor hearts were compared with those accepted and revealed the following predictors for non-use: donor age >50 years old, female donor, hypertension, diabetes mellitus, ejection fraction <50%, and cerebrovascular
cause of death. These variables were similar among the 11 existing UNOS regions, despite differences in organ procurement rates. What remained unknown was whether discarding these hearts prevented poor outcome.

A 15-point donor risk score predicting recipient survival was developed using the UNOS database. The cohort included all adult heart transplant recipients from 1996 to 2007. Eighty percent of the sample was used to create the derivation cohort, whereas 20% was utilized as the validation set. All plausible donor variables predicting 1-year mortality were evaluated, and the final model included ischemic time, donor age, race mismatch, and urea nitrogen/creatinine ratio ≥30. Ischemic time posed the highest mortality risk followed by age, renal function, and then race mismatch. The model predicted 1- and 5-year post-heart transplant mortality and provided a potential opportunity for centers to determine whether a marginal donor heart was acceptable. A similar model was developed in Europe called the European Transplant Heart Donor Score. Although only 2 variables (age and left ventricular hypertrophy) in that model were independent predictors of mortality, a composite Heart Donor Score above 17 was associated with higher risk of 3-year mortality after transplantation.

Can marginal hearts be resuscitated and re-evaluated? In 2002, the Crystal City Consensus Conference Report provided recommendations for hormonal therapy and hemodynamic monitoring to recover donor hearts with abnormal ventricular systolic function. After resuscitation with hormones, fluids, inotropes, and vasopressors, a donor heart was deemed acceptable if the Papworth criteria were met: mean arterial pressure >60 mm Hg, central venous pressure 4 to 12 mm Hg, pulmonary capillary wedge pressure 8 to 12 mm Hg, systemic vascular resistance 800 to 1200 dyne/s·per cm², cardiac index >2.4 L/min-per m², and dopamine <10 μg/kg-per min or dobutamine <10 μg/kg-per min. The Papworth criteria were chosen because in Great Britain, 92% of organs that failed to meet transplant criteria on initial evaluation were successfully resuscitated, and 84% of those donors were successfully transplanted. Although high-dose inotrope support to maintain adequate hemodynamics was considered unfavorable, data now suggest acceptable outcomes after heart transplantation. More research is needed to further explore increasing utilization of marginal donors after resuscitation, especially because new technology like ex-vivo perfusion can potential improve donor suitability.

Figure 2. Interaction between donor left ventricular hypertrophy and ischemic time on post-transplant survival. Reprinted from Wever Pinzon et al32 with permission. Copyright © 2011, John Wiley and Sons.

Figure 3. Cardiac Transplant Research Database: adults heart transplantation and the effect of donor hypertension (A) or diabetes mellitus (B) and sex. The cohort consists of 7322 patients from 32 heart transplant centers who were transplanted between 1990 and 2007. Reprinted from Stehlik et al33 with permission. Copyright © 2010, Elsevier.
Heart Transplant Waitlist
The number of candidates added to the waitlist every year has increased by 34% since 2003 and is almost twice the number of hearts actually implanted, which has not significantly changed for the past 15 years (see Figure 4).\(^{39}\) Candidates are now older\(^{39}\) and with more comorbidities. Even active tobacco use is permitted (considered Class IIa relative contraindication), and there are no boundaries to exclude and define issues like end-organ damage for diabetes mellitus.\(^{6}\) The result is an increasing number of patients expecting heart transplantation and too few donors to meet the demand. The lifeboat for advanced heart failure will sink if it attempts to hold everyone.\(^{40}\)

Reducing the Waitlist
There are 2 ways to reduce the waitlist: (1) standardize eligibility criteria and (2) prevent patients ineligible at one center from seeking listing at another. Eliminating eligibility for certain subgroups is difficult. Decisions should be based on data to support poorer outcomes such as age ≥70 years,\(^ {41}\) active tobacco abuse,\(^ {42,43}\) renal insufficiency,\(^ {41}\) and possibly bailout transplant for complications with ventricular assist device (VAD) initially implanted as destination therapy. Ethical issues to address are listing stable patients (currently listed as UNOS Status 2),\(^ {44}\) dual organ transplantation, retransplantation, foreign nationals (transplant tourists),\(^ {45}\) and maintaining the rule for UNOS Status 1A for 30 days among patients with permanent mechanical assist devices that are stable and without complications.\(^ {46}\) The arguments against these ethical concerns are many. Not all ambulatory UNOS Status 2 patients are the same. Some are more walking wounded and unstable than others. Dual organ transplantation is possible with good results, and the life of one person should not be deemed less important than 2 people. Retransplantation is necessary for children who undergo transplant at earlier ages to survive into adulthood. Foreign nationals often come to United States because their country does not provide transplantation. Finally, the need to maintain UNOS Status 1A exception for 30 days after implantation of VADs is to increase the opportunity to remove the device before a complication ensues.

Heart Transplant Allocation
Allocation for OHT is based primarily on severity of illness. It began as a 2-tiered system in 1988 and was changed to a 3-tiered system in 1998.\(^ {37}\) Selection criteria for the 3-tiered system are the following: UNOS Status 1A (high priority), 1B (intermediate priority), and 2 (low priority). This allocation scheme was adequate in 1999 when the data supported a high mortality rate for UNOS Status 1A patients. However, the mortality gap has narrowed with advancements in mechanical circulatory support,\(^ {34}\) medical therapy,\(^ {49,50}\) and device therapy (see Figure 5).\(^ {51-53}\) Consequently, a new allocation scheme has been proposed and currently is open for public comment.

Inadequacies
There are many inadequacies in the current allocation system. For example, the UNOS criteria for heart transplantation reflect medical urgency, but no objective data are required to justify advanced heart failure care. For instance, in the current allocation system, UNOS Status 1B is reserved for patients on continuous intravenous inotropes or with VAD support, yet no data strictly defines who qualifies for these treatment options. The ambiguity provides a loophole and makes gaining the system possible. To minimize this potential abuse, other organ allocation systems have relied predominately on objective data. For example, the Model for End-Stage Liver Disease score for liver transplantation is derived from serum laboratory values,\(^ {54}\) and the lung allocation score for lung transplantation relies mostly on objective data.\(^ {55}\) For heart transplantation, hemodynamic criteria for cardiogenic shock is necessary and has been proposed in the new heart transplant allocation scheme.

There are other concerns with the current allocation system. These include race/ethnicity,\(^ {56}\) sex,\(^ {57}\) type of cardiomyopathy,\(^ {47,58,59}\) and geographic disparities.\(^ {60}\) A large study including over 10000 patients listed for heart transplant in the United States between 2006 and 2010 identified Hispanics as having a higher risk of death or removal from the waitlist compared with whites (hazard ratio 1.51, 95% confidence interval 1.23–1.85). After adjusting for many baseline differences, Hispanics remained 51% more likely than whites to either die or be removed from the waitlist because of severity of illness. Blacks, on the contrary, had similar prognosis as whites while waiting for transplantation (hazard ratio 1.13, 95% confidence interval 0.97–1.31).\(^ {56}\)

Women have a higher waitlist mortality than men (see Figure 6) despite shorter waiting times until heart transplantation\(^ {61}\) and similar survival with rescue techniques, such as mechanical circulatory support.\(^ {48}\) The reasons for this discrepancy remain unclear. In one small European study (58 women and 260 men), women had a higher risk of death/deterioration than men after adjusting for age, Heart Failure Survival Score, creatinine, inpatient status, cardiac index, low vocational level, smoking, and low emotional support at time of transplantation (adjusted hazard ratio 2.3; 95% confidence interval 1.04–5.12; \(P=0.04\)).\(^ {62}\) In a large US study with over 28000 patients, the higher risk for women appeared to be limited to UNOS Status 1A (adjusted hazard ratio 1.245, 95% confidence interval 1.095–1.415; \(P=0.0008\)) despite similar levels of severity at time of listing.\(^ {57}\)

Figure 4. Scientific Registry of Transplant Recipients: total patients awaiting and receiving heart transplantation from 2002 to 2013. Adapted from Colvin-Adams et al\(^ {28}\) with permission. Copyright © 2013, John Wiley and Sons. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
Patients with restrictive cardiomyopathy, congenital heart disease, and congenital heart disease seem to be at a disadvantage when compared with nonischemic and ischemic cardiomyopathy patients awaiting transplantation. Few of these patients qualify for VAD support, making it challenging to bridge them to transplantation. For example, congenital heart disease patients compared to non–congenital heart disease have a higher 2-month mortality on the waitlist after multivariate analysis and no survival benefit with VAD support. These patients have been recognized in the new allocation scheme as a disadvantaged group and will be included at a higher tier.

There also is disparity between availability of donors and location of patients awaiting transplantation. There are currently 58 donation service areas distributed within 11 transplant regions in the United States. Some regions are heavily populated and have long waiting time for transplantation, while other regions have more donors than available local recipients. This geographic disparity has raised many concerns.

**Possible Alternatives**
The Organ Procurement and Transplantation Network / UNOS Heart Subcommittee had reviewed several options to improve the current allocation system. They published their plan to consider adding more tiers and proposed a more granular rule-based system with 6 active tiers instead of 3. Although this system will be an improvement, the risk factors associated with each category have not been identified to improve optimal timing for consideration of urgent transplantation. For instance, although restrictive cardiomyopathy will be deemed high risk, it remains unclear when these patients should be considered for urgent transplant rather than at a lower tier? A major issue will be that some of these groups have a higher mortality after transplant also. In general, giving highest priority to the highest pretransplant risk patients makes sense until the 1-year post-transplant mortality approaches 50%.

An alternative plan would be to eliminate low-risk tiers to match the market with those at highest risk for death. If low-risk ambulatory patients were removed from the waitlist and registered to facilitate transplantation after they deteriorate, the expectations of the patient and medical providers would be better served because in 2014, only 107 patients were transplanted as UNOS Status 2. Low-risk patients could include stable heart failure patients with peak Vo2 12 to 14 mL/kg per min and no implantable cardioverter defibrillator shocks. This elimination of a tier would make a small impact on matching the market (only 4.7% transplanted as UNOS Status 2).
in 2014) but a large impact on matching expectations of patients with likelihood of being transplanted.

Another consideration is to create an allocation score. This would change a rule-based system to an algorithmic-based system. Algorithmic-based systems can predict waitlist mortality, such as the Model for End-Stage Liver Disease score used for liver transplantation. They can also be constructed to predict both pre- and post-transplant mortality to minimize death on the waitlist and yet prevent futility, such as the lung allocation score for lung transplantation. To create an algorithmic-based allocation system, risk factors must be identified. This task is possible but would be substantial given the number of high-risk groups potentially present and possible interactions with many variables.

Geographic disparity can be reduced by either transporting people or organs across current UNOS regions. Relocating organs may be possible. However; relocating patients is often limited to more affluent individuals, which raises ethical concerns given the need to keep organ allocation fair and equitable to all. Another alternative to reducing geographic disparity is to broaden sharing or reorganize regions to better match the population density with donor availability. The liver transplant allocation system is considering restructuring their program from 11 regions to either 4 or 8 to better meet the population density with donor availability. The use of VADs or listing for transplantation should be considered in Interagency Registry for Mechanically Assisted Circulatory Support Profile 5 patients, who are comfortable at rest but have minimal functional reserve, as documented by peak VO$_2$ <12 to 14 mL/kg per min. More research will need to be done to better identify this cohort.

VADs provide an important alternative to transplantation. They have been proven to extend life for both women and men with advanced heart failure and shown to be superior to medical therapy for Interagency Registry for Mechanically Assisted Circulatory Support level 4–7. Currently, devices are implanted for bridge to transplant and less frequently as destination therapy. In fact, many who are labeled as destination therapy are later switched to bridge to transplantation. The lack of enthusiasm for embracing VADs as permanent alternatives to transplantation is because of the risk of pump thrombosis, stroke, and driveline infections. So who should receive VADs as an alternative to transplantation? VADs are indicated for patients who are Interagency Registry for Mechanically Assisted Circulatory Support profile 4 or worse, with consistent symptoms of heart failure at rest or minimal activity. The use of VADs or listing for transplantation should also be considered in Interagency Registry for Mechanically Assisted Circulatory Support Profile 5 patients, who are comfortable at rest but have minimal functional reserve, as documented by peak VO$_2$ <12 to 14 mL/kg per min. More research will need to be done to better identify this cohort.

**Conclusions**

Strategies to better match the market for heart transplantation are necessary to enable a scarce resource to be maximally used. There are 3 ways to achieve this goal: (1) increase the donor pool, (2) reduce the waitlist, and (3) improve the allocation system. Although it is easier to focus national efforts on only one strategy, all must be done simultaneously to ensure that the growth of the waitlist matches the number of available donors. Advances in technology should provide better opportunity to engage young people to become organ donors, such as Facebook. Other social media needs to be explored and more successful programs like state revenue generated by organ donors who opt-in. Although it is not clear which method is best in the United States, it is clear that the best donor is young and healthy. Family members are likely to be distraught and surprised when a young person dies and less likely to donate organs voluntarily. Therefore, it may be best to figure out how to have more of these potential donors opt-in and make it clear before death their wishes to be an organ donor. The waitlist also needs to be reduced, and strict uniform criteria based on outcome data will need to be used. This will likely be the most difficult aspect. Just because we can transplant a patient with multiple comorbidities or tobacco abuse, we need to remember that we have a limited resource that should be distributed to only those with the best outcome for success. Finally, efforts to improve the allocation system need to be embraced. Objective data to define tiers in my opinion will prevent gaming the system, and research needs to be done to better determine optimal timing for urgent transplantation in high-risk groups like restrictive cardiomyopathy. Alternatives to transplant like the usage of VADs should be considered.

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**Figure 7.** Scientific Registry of Transplant Recipients waiting list based on type of cardiomyopathy. Reprinted from Hsich et al with permission. Copyright © 2014, Elsevier.
especially once patients are identified that have similar survival with either option. Finally, collaboration between many medical and community participants will be vital to begin the rematch between supply and demand as we strive for more effective allocation of the scarce resource of human hearts for transplantation.

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